Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Identification of Perinatal HIV Exposure (Updated August 11, 2011)

Panel's Recommendations:
• HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
• Repeat HIV testing in the third trimester is recommended for women who have negative HIV antibody tests earlier in pregnancy if they are at high risk of HIV infection because of behavior or residence in a high-prevalence area **(AII)**.
• Women seen at labor with undocumented HIV status should undergo rapid HIV antibody testing, and women with a positive antibody test should initiate intrapartum antiretroviral (ARV) prophylaxis **(AII)**.
• If acute HIV infection is suspected in a pregnant woman, a virologic test (e.g., plasma HIV RNA assay) should be performed because serologic testing may be negative at this early stage of infection **(AII)**.
• Women who have not been tested for HIV before or during labor should undergo rapid HIV antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing. If the mother or infant is HIV antibody positive, infant ARV prophylaxis should be initiated as soon as possible and the mother advised not to breastfeed pending results of confirmatory HIV antibody testing **(AII)**.

Diagnosis of HIV Infection in Infants (Updated August 11, 2011)

Panel's Recommendations:
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months **(AII)**. HIV antibody testing cannot establish HIV infection in this age group because maternal HIV antibodies may persist and interfere with the interpretation of a positive HIV antibody test.
• Virologic diagnostic testing is recommended in infants with known perinatal HIV exposure at ages 14–21 days, 1–2 months, and 4–6 months **(AII)**.
• Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection **(BIII)**.
• HIV DNA polymerase chain reaction (PCR) and HIV RNA assays are recommended as preferred virologic assays **(AII)**.
• Confirmation of HIV infection should be based on two positive virologic tests obtained from separate blood samples **(AI)**.
• Definitive exclusion of HIV infection (in the absence of breastfeeding) should be based on at least two negative virologic tests (one at >1 month and one at ≥4 months of age) **(AII)**.
• Some experts confirm the absence of HIV infection at 12–18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
• In children ≥18 months of age, HIV antibody assays alone can be used for diagnosis **(AII)**.

Laboratory Monitoring of Pediatric HIV Infection Before Initiation of Therapy (Updated August 11, 2011)

Panel's Recommendations
• The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or count and plasma HIV RNA level **(AII)**. For any given CD4 percentage or count, younger children, especially those in the first year of life, face higher risk of progression than do older children.
• In children younger than 5 years of age, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group **(AII)**.
• CD4 percentage or count should be measured at the time of diagnosis of HIV infection and at least every 3-4 months thereafter **(AIII)**.
• Plasma HIV RNA should be measured to assess viral load at the time of diagnosis of HIV infection and at least every 3-4 months thereafter **(AIII)**.
• More frequent CD4 cell and plasma HIV RNA monitoring should be considered in children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(AIII)**.

Antiretroviral-Naive HIV-Infected Infants 12 Months or Younger

Panel's Recommendations (Table 7)
• Antiretroviral therapy (ART) should be initiated in HIV-infected infants <12 months of age, regardless of clinical status, CD4 percentage, or viral load **(AII)**..
• Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before therapy is initiated **(AIII)**.

Antiretroviral-Naive HIV-Infected Children 1 Year or Older

Panel's Recommendations (Table 7)
• Antiretroviral therapy (ART) should be initiated in children age ≥1 year with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or plasma HIV RNA level **(AI*)**.

• Initiation of ART is also recommended for children age ≥1 year regardless of symptoms or plasma HIV RNA level if:
  • age 1 to <5 years and CD4 percentage <25% **(AII)**; or
  • age ≥5 years and CD4 count ≤500 cells/mm^3 (**AI*** for CD4 percentage <25% or CD4 count <350 cells/mm^3 and **BII*** for CD4 count 350–500 cells/mm^3).

• Initiation of ART is also recommended for children age ≥1 year who are asymptomatic or have mild symptoms (Clinical Categories N and A or a single episode of serious bacterial infection) with a plasma RNA ≥100,000 copies/mL regardless of CD4 percentage/count **(BII*)**.
• Initiation of ART may be considered for children age ≥1 year who are asymptomatic or have mild symptoms with a plasma RNA RNA <100,000 copies/mL and CD4 percentage >25% if age 1–5 years or CD4 count >500 cells/mm^3 if age ≥5 years **(CIII)**.

What Drugs to Start: Initial Combination Therapy for Antiretroviral-Naive Children (Updated August 11, 2011)

Panel's Recommendations
• Combination therapy, including either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, is recommended for initial treatment of HIV-infected children **(AI)**.
• The goal of therapy in treatment-naive children is to reduce plasma HIV RNA levels to below the limits of quantitation of ultrasensitive assays and to preserve or normalize immune status **(AI)**.
• Antiretroviral (ARV) drugs initiated for chemoprophylaxis of mother-to-child (MTCT) transmission of HIV should be discontinued in infants who are identified as HIV infected **(AI)**.
• ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive children (**AII** infants; **AIII** children).

Monitoring of Children on Antiretroviral Therapy (Updated August 11, 2011)

Panel's Recommendations
• Within 1-2 weeks of starting a new antiretroviral (ARV) regimen, children should be evaluated to screen for clinical side effects and to ensure patient/caretaker adherence to the regimen **(AIII)**. Evaluations can be conducted in person or over the phone.
• Following initiation or change in therapy, more frequent evaluation may be needed to support adherence to the regimen **(AIII)**.
• At least every 3-4 months thereafter, children should have a monitoring evaluation to assess both effectiveness and potential toxicity of their ARV regimens **(AII*)**.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents (Updated August 11, 2011)

Panel's Recommendations
• Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent. Adolescents with perinatal infection generally have a very different clinical course and treatment history than those who acquired HIV during adolescence **(AIII)**. • Appropriate dosing of antiretroviral (ARV) medications for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and physiologic development **(AII)**. • Effective and appropriate contraceptive methods for adolescence should be selected to reduce the likelihood of unintended pregnancy and to prevent transmission of HIV to sexual partners **(AI)**. • Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**. • Efavirenz should not be used by an adolescent female who desires to become pregnant or who does not use effective and consistent contraception **(AII)**. Efavirenz also should not be used throughout the first trimester of pregnancy **(AII)**. • Pediatric and adolescent care providers should prepare adolescent patients for the transition into adult care settings **(AIII)**.

Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated August 11, 2011)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again prior to changing regimens **(AIII)**. • Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**. • At least one method of measuring adherence to ART (e.g., quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load **(AII)**. • When feasible, once-daily antiretroviral (ARV) regimens should be prescribed **(AI*)**. • To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with the patient/caregiver, and identify mutually acceptable goals for care **(AII*)**.

Management of Medication Toxicity or Intolerance (Updated August 11, 2011)

Panel's Recommendations
• If a child has severe or life-threatening toxicity, all components of the drug regimen should be stopped immediately **(AIII)**. Once the symptoms of toxicity have resolved, antiretroviral therapy (ART) should be resumed with substitution of a different antiretroviral (ARV) drug or drugs for the offending agent(s) **(AII*)**.
• When changing therapy because of toxicity or intolerance to a specific drug in a virally suppressed child, changing a single drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side effect profile should be chosen **(AI*)**.
• The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity to facilitate future medication choices if care is transferred **(AIII)**.
• Dose reduction is not a recommended option in the setting of ARV toxicity except when therapeutic drug monitoring (TDM) indicates a drug concentration above the normal therapeutic range **(AII*)**.

Antiretroviral Treatment Failure in Infants, Children, and Adolescents (Updated August 11, 2011)

Panel's Recommendations
• The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay **(AI*)**.
• When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and preserve future antiretroviral (ARV) options **(AII)**.
• Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy **(AII)**.
• Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

Approach to the Management of Virologic Failure of Antiretroviral Treatment

Panel's Recommendations
• The causes of treatment failure, which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions, should be assessed and addressed **(AII)**.
• A consensus on how to treat immunologic failure or clinical failure in the setting of sustained virologic suppression does not exist **(AIII)**.
• When deciding how to treat a child with virologic treatment failure, the probability of achieving durable virologic suppression should be considered as well as the future options for treatment should durable suppression not be achieved **(AII)**.
• Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance

Panel's Recommendations
• Antiretroviral (ARV) regimens should be chosen based on treatment history and drug-resistance testing, including past and current resistance test results **(AI*)**.
• Ideally, the new regimen should include three fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results **(AII*)**. Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist **(AI*)**.
• Use of novel agents with limited available pharmacokinetic (PK) and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist **(AIII)**.

The Use of Antiretroviral Agents Not Approved for Use in Children

Panel's Recommendations
• Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age range because many of the recently approved, more convenient, and potent agents are approved for use in adults before pharmacokinetic (PK), safety, and efficacy data are available in children **(AII)**.
• "Off-label" use of ARVs in children can be risky because, pending pediatric dosing recommendations, dosing often cannot be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Off-label use of ARVs should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and PKs of ARVs that are not yet Food and Drug Administration (FDA) approved for children **(AI*)**.
• Whenever possible, use of ARVs that are not yet FDA approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval **(AIII)**.

Antiretroviral Drug-Resistance Testing (Updated August 11, 2011)

Panel's Recommendations
• Antiretroviral (ARV) drug-resistance testing is recommended before initiation of therapy in all treatment-naive children **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
• ARV drug-resistance testing is recommended before changing therapy for treatment failure **(AI*)**.
• Resistance testing in the setting of virological failure should be obtained while the patient is still on the failing regimen or within 4 weeks of discontinuing the regimen **(AII*)**.
• Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ARV therapy regimens **(BIII)**.
• The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, especially if the ARV agent shares cross resistance with drugs previously used. In addition, current resistance assays are not sensitive enough to fully exclude the presence of resistant virus. Thus, previously used ARV agents and previous resistance test results should be reviewed when making decisions regarding the choice of new agents for patients with virologic failure **(AII)**.
• Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered **(AI*)**. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist **(AI*)**.
• Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an ARV regimen in a pediatric patient **(AI*)**.